

A New Landscape for Combatting Infectious Diseases

Advances in science and technology aimed at identifying the complete genetic makeup of microorganisms are ushering in a new era for controlling infectious threats. By using genetic sequencing to examine infectious pathogens, these technologies are on the verge of revolutionizing our ability to diagnose infectious diseases, investigate and control outbreaks, understand transmission patterns, develop and target vaccines, and determine antimicrobial resistance—all with increased timeliness and accuracy and decreased costs. Recent reports have highlighted early efforts on the use of whole-genome sequencing (WGS) technologies in investigating outbreaks of drug-resistant bacteria in hospitalized patients at the National Institutes of Health Clinical Center and in the United Kingdom (**Box 1**), an outbreak of foodborne disease in Europe, and an outbreak of tuberculosis in Canada. Termed “genomic epidemiology,” this approach to infectious disease control was named one of the six “**Areas to Watch in 2012**” by the journal *Science* on the basis of its transformative potential in “**determining quickly where newly emerging diseases come from, whether microbes are resistant to antibiotics, and how they are moving through a population.**”

New opportunities bring new challenges

Along with the many opportunities afforded by these “next-generation” sequencing technologies come new responsibilities and challenges for clinical and public health. In particular, the availability and ease-of-use of WGS technology is rapidly changing the way that diseases are studied—providing a new level of detailed information to better understand how infections occur and are transmitted.

The major benefit of genomic sequencing is its ability to rapidly generate massive amounts of data on a pathogen. **A key component in the usefulness of these technologies, however, is ensuring the availability of sufficient laboratory and computing infrastructure (i.e., “bioinformatics”) and highly skilled experts to manage, analyze, evaluate, and gain new information from (i.e., make sense of) these large amounts of biological data.**

CDC is requesting dedicated FY 2014 funding to develop and incorporate new molecular technologies and bioinformatics capacities into public health—improving infectious disease control efforts by CDC and its public health partners. CDC’s current capacities in these areas are not sufficient to meet the challenges of this rapidly evolving field, threatening the Agency’s ability to meet its public health mission.

Ensuring continued public health capacity at CDC

The Centers for Disease Control and Prevention (CDC) is recognized and relied upon nationally and globally for its strong epidemiologic and laboratory expertise and capacity for controlling infectious diseases, with laboratory reference capability for virtually all human infections. Ensuring that CDC can continue to meet its responsibilities is a critical public health priority. Because of resource constraints, CDC has not been able to develop the bioinformatics capacity to keep pace with the rapidly growing field of molecular diagnostics.

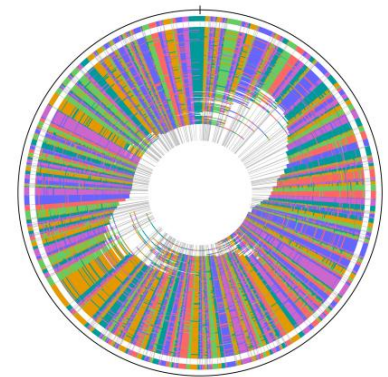
To better identify gaps and make recommendations for best use of Agency resources in meeting these challenges, CDC convened a panel of external experts in bioinformatics, informatics, and laboratory information technology in 2011 to review the status of this technology at CDC and its ability to meet programmatic needs. Among their feedback was a clarion call for urgent action:

*CDC is known for its strong ability to accurately analyze and interpret disease surveillance data. However, the Agency runs the risk of going from **outdated to obsolete and then to irrelevant** without strong investments in the science of bioinformatics . . .*



Expanding molecular technologies and bioinformatics capacities at CDC

The expert panel recommended both short-term and long-term goals to meet the most urgent needs and opportunities and to ensure that CDC's capacities in these areas become “**sustainable resources for public health.**” CDC has worked to address several of the short-term goals, including developing a nascent bioinformatics program to provide initial support for evolving scientific needs. Among its activities, this core group has worked with programs across CDC's infectious disease laboratories to identify priorities and to strengthen collaborations with outside agencies and partners. Examples of priority areas include the following:



Genomic mapping of
Legionella pneumophila serogroup 8

■ Bioinformatics Program Development

- Enhancing CDC's bioinformatics expertise and infrastructures
- Working with partners to establish bioinformatics training fellowships to meet future workforce needs

■ Next-Generation PulseNet (Box2)

- Modernizing PulseNet to encompass whole genome sequencing technologies to improve our ability to detect and respond to foodborne disease outbreaks
- Expanding the use of these new capacities to other CDC national infectious disease surveillance networks

■ The Research Grade Network

- Establishing a separate information technology network for use by CDC laboratories and their public health partners
- Ensuring broader access to and facilitating rapid exchange of laboratory and bioinformatics information and datasets

■ MicrobeNet

- Creating a system of web-accessible, searchable databases containing detailed, reference information to characterize infectious pathogens
- Ensuring near real-time analysis and feedback of information on submitted pathogens for CDC and its local, state, national, and international laboratory partners

Advances in molecular-based technologies along with enhanced bioinformatics capacities generate a new level of information on infectious pathogens that can be used to more accurately and rapidly

- *Diagnose infectious diseases*
- *Investigate and control outbreaks*
- *Understand transmission patterns*
- *Determine antimicrobial resistance*
- *Develop and target prevention measures, including vaccines*

It is critical for CDC to have the molecular tools and bioinformatics capacity to provide expertise and leadership in ensuring that the expanding use of these technologies translates into effective information for guiding public health action.

Now and into the future

Molecular-based technologies represent an evolving and rapidly changing field. While the potential for their use across a wide range of specialties continues to evolve, at present they are on a course to totally reshape the practices of microbiology and infectious disease control. As the use of these technologies extends to more and more clinical and laboratory settings, it is critical for CDC to have the molecular tools and bioinformatics capacity to provide expertise and leadership in ensuring that the expanding use of these technologies translates into meaningful information to guide effective public health action.



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Box 1. New Approaches to Reducing Healthcare-Associated Infections and Detecting Antibiotic Resistance

More than 1 million healthcare-associated infections (HAIs) and 100,000 related deaths occur in the United States each year. At any given time, approximately 1 in 20 patients receiving treatment in U.S. hospitals has an HAI. In addition to their tremendous toll on human health, these largely preventable infections add billions of dollars to healthcare costs each year. Although much progress towards reducing these infections has been made over the last several years, HAIs remain all too common. Complicating control efforts is the increasing number of outbreaks that involve drug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and even more difficult-to-treat, gram-negative bacterial infections such as *Escherichia coli* and *Klebsiella pneumoniae*. These gram-negative infections are increasingly resistant to most available antibiotics and can also pass along genetic materials that enable other bacteria to become drug-resistant. With new resistant strains being identified across a spectrum of healthcare-associated, foodborne, respiratory, STD, and other infections, advances in genomic sequencing can play a critical role in rapidly identifying these infections, tracking their spread, and improving control measures.

Use of WGS in Investigating Outbreaks of HAIs

Whole-genome sequencing (WGS) technology has been used to investigate several outbreaks of drug-resistant HAIs. For one investigation, researchers in the United Kingdom used whole-genome sequencing to re-examine an outbreak of MRSA that had occurred earlier in a neonatal unit. Because traditional methods of subtyping are not able to clearly identify related MRSA infections, the researchers looked to WGS to better define the infections and determine transmission linkages. The data identified a cluster of associated infections as well as separate infections not linked to the outbreak. Although this investigation was performed retrospectively, it highlighted the potential use of WGS in providing timely and highly accurate information to better guide patient care and to improve infection control.

Another recent investigation involved the use of WGS to help investigate the spread of carbapenem-resistant *K. pneumoniae* among patients at the National Institutes of Health Clinical Center, after introduction of the highly resistant infection from a woman transferred to the center to participate in a clinical trial in 2011. Despite intensive infection control efforts, including almost immediate isolation of the index patient, the bacteria began to appear in patients across other areas of the center. Many of these individuals died—some from their underlying illness and others from the infection. Again, current typing methods are not able to distinguish differences in *K. pneumoniae*, so it was unclear whether all the patients were infected with the same strain. Medical staff reached to researchers at the National Human Genome Research Institute, who used genomic sequencing to help determine how the infection spread. The sequencing showed that all of the cases likely originated from the index patient, with the infections transmitted from bacteria on at least two different sites on her body during at least three separate events—providing important information for changing and implementing new infection control measures.

Leveraging Molecular Technologies to Advance Public Health

CDC has strong expertise in the areas of HAIs and antimicrobial resistance. In fact, CDC's leadership in reducing HAIs through targeted educational and infection control efforts; improved means of reporting and tracking infections and evaluating control efforts; and increased involvement of states in these prevention efforts has helped the nation achieve dramatic results in this area, with reductions of nearly 60% in the occurrence of certain types of healthcare-associated bloodstream infections. CDC's extensive and highly successful infectious disease surveillance networks have been developed over the years with clinical, laboratory, and public health partners across the nation and globally. These surveillance platforms are poised to leverage WGS and other molecular technology advancements in new and exciting ways to improve public health.

Advances in genomic sequencing can play a critical role in rapidly identifying HAIs and tracking their spread—providing important information for improving control measures. CDC's extensive and highly successful infectious disease surveillance networks, involving clinical, laboratory, and public health partners across the nation and globally, are poised to leverage these technologies in new and exciting ways to improve public health.

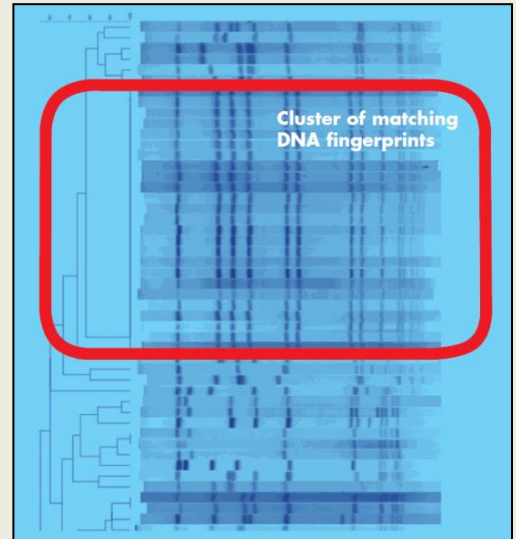


Box 2. Expanding the Use of Molecular Technologies to Improve Food Safety: *Next-Generation PulseNet*

An estimated 48 million foodborne illnesses occur in the United States each year, resulting in 128,000 hospitalizations and 3,000 deaths. CDC tracks and investigates foodborne diseases in collaboration with state and local health departments and other partners, working to rapidly identify their sources and contain their spread. Essential to these efforts is PulseNet, a network of state and local public health and food regulatory agency laboratories across the United States and internationally that work to identify similar cases of foodborne illnesses that might signal an outbreak. Over the past 15 years, PulseNet has revolutionized our ability to detect clusters of foodborne illness, detecting hundreds of outbreaks, enabling faster and better responses, and leading to important improvements in food safety.

Enabling Real-time Communication on Foodborne Illness

PulseNet's national network of more than 80 state and federal laboratories use pulsed-field gel electrophoresis (PFGE) to examine DNA patterns of bacterial infections—a technology that has been used for decades. These laboratories submit PFGE patterns from bacteria of persons with foodborne infections to a CDC database for rapid comparison of strains of organisms such as *Escherichia coli* O157:H7, *Salmonella*, *Shigella*, *Listeria*, and *Campylobacter*. Each year, approximately 50,000 DNA fingerprints are uploaded into the PulseNet database. Today, **this laboratory network tracks a cumulative database that represents nearly half a million bacterial isolates from food, the environment, and persons with foodborne illness.** In addition to allowing for real-time communication among CDC, state and local health departments, and international partners, PulseNet also helps food regulatory agencies identify areas needing additional food safety measures by linking bacteria causing illnesses in people to bacteria detected in food.



Modernizing PulseNet to Meet the Demands of Next-Generation Sequencing Technologies

Like many of our public health disease surveillance networks, PulseNet relies on isolates from culture-based testing methods, the long-held standard in testing of specimens from patients with foodborne and other infections. However, more and more diagnostic tests that do not use culture are being developed and marketed for clinical use, including use by clinical laboratories in diagnosing foodborne infections. Because of their reduced costs, rapid turnaround times, and less labor-intensive methodology, these tests may soon replace culture-based tests, necessitating fundamental changes in our public health efforts to track and control infectious diseases. Modernizing PulseNet to meet these challenges through new technologies and expanding laboratory capabilities is a priority for CDC. The need for enhanced capacity extends beyond PulseNet, however, to other national surveillance systems such as the National Antimicrobial Resistance Monitoring System. Fortunately, building the bioinformatics and laboratory infrastructure to support these new technologies for one surveillance system can serve as a platform for their use across other systems.

Laboratories play an important role in stopping contaminated food from reaching the public. Ensuring that PulseNet and other national infectious disease surveillance systems incorporate the molecular and bioinformatics technologies that are reshaping the practices of microbiology and infectious disease control is a critical priority for CDC and public health.

As the use of these next-generation sequencing technologies continues to expand, it is essential that CDC's national surveillance systems and laboratory infrastructure encompass the technology to ensure that infectious disease surveillance efforts are standardized and to enable CDC and its public health partners to most accurately detect, respond, and implement actions to contain newly emerging and well-recognized infectious threats regardless of their source.

